REMARKS/ARGUMENTS

Applicants thank the Examiner and her supervisor for conducting an interview with their attorneys on February 8. At the interview, references by Guerney, US 6,420,534, Powell, US6,319,689, and Chrysler, US 5,744,346 were discussed. Regarding Guerney, applicants noted that because all of the present claims are entitled at least to a priority date of June 15 via provisional application No. 60/139,172, filed June 15, 1999 (see attached chart), Guerney was only citable under 35 USC 102(e) insofar as the disclosure of the '534 patent was reproduced in the priority application (USSN 60/101,594 filed September 24, 1998). It was pointed out that the priority document of Guerney (USSN 60/101,594 filed September 24, 1998) differed in many respects from the granted patent. Particularly, the priority document misidentifies the location of the transmembrane region of its isolated aspartyl protease (see p. 20), does not identify the signal sequence or pro region occupying amino acids 1-21 and 22-45 of the protein, misidentifies the function of its aspartyl protease as gamma secretase (see title), and does not express its aspartyl protease as a protein. It was further pointed out that in an office action in Guerney application 09/548,368, Examiner Turner rejected Guerney's arguments (presented by declaration) that he was entitled to priority for the "location of the transmembrane domain, or particular mutant lacking specific residues corresponding to the transmembrane domain and for deletion mutant lacking such specific residues which retain activity." Copies of the Guerney priority document, the declaration presenting Guerny's argument and the office action holding Guerney was not entitled to priority, as noted above, are cited on the attached supplemental IDS to complete the record.

It was further pointed out at the interview that Powell discusses a sequence of an aspartyl protease that differs from present SEQ ID NO:2 at codon 130. It was also pointed out that Powell does not identify his aspartyl protease as being beta secretase, or identify the transmembrane, signal or pro regions within it. It was further pointed out that the purity of beta secretase obtained by Chrylser was about 200-fold less than the present case. It was also pointed

out that the purification to homogeneity disclosed in the present case was achieved using affinity chromatography with a specific inhibitor (see Example 7 at p. 75) not discussed by Chrysler.

Claims 1, 15, 18, 22-25, 29-31, 33-34, 36, and 132-133 are pending and have been previously examined. Claim 134 is added. Claims 2-14, 16-17, 19-21, 26-28, 32, 35, and 37-131 have been canceled. Support for the amendment to recite a segment comprising residues 63-452 in claim 1 is provided e.g., p. 30 second sentence and p. 8, line 24. Claim 1 has also been amended for improved clarity simply to recite lack of residues 1-45 rather than previously reciting lack of residues 1-21 and 22-45. Support for new claim 134 is provided by e.g., claim 24 as filed and page 11, line 13. No claim amendment should be construed as an acquiescence in any ground of rejection.

35 U.S.C. § 112, Second Paragraph

Claim 18 has been amended to replace "with respect to SEQ ID NO: 2" with "of SEQ ID NO: 2."

Claim 13 has been canceled. Claims 33 and 34 have been amended to specify the transitional term "consisting of."

Claim 32 has been canceled.

Claim 33 has been amended to delete reference to conservative substitutions.

35 U.S.C. § 112, First Paragraph

Claim 1 and the claims depending therefrom

Independent claim 1 and the claims depending therefrom have been rejected as allegedly failing to comply with the written description requirement. The Examiner takes the position that the disclosure of particular fragments having beta-secretase activity does not convey possession of the whole genus. In response, the claim has been amended to specify that the protein comprises residues 63 to 452 of beta-secretase but lack residues 1-45. The claims as amended define a genus of proteins by a specific structural feature (i.e., presence of at least residues 63-452), thereby distinguishing the claimed proteins from other proteins, and satisfying the written description requirement.

Claims 32, 33 and 34 are also alleged to lack written description in that the claims include a genus of peptides only one species of which is disclosed in the specification. To expedite prosecution, applicants have cancelled claim 32 and amended claims 33 and 34 so that they refer to the species disclosed in the specification for which written description has not been questioned.

Independent claim 1 and the claims depending therefrom have been rejected because although the specification enables determining whether a segment of beta-secretase is active, the claims are not limited to proteins having the beta-secretase function. As discussed above, the claims have now been amended to define the claim proteins as comprising residues 63-452 of SEQ ID NO:2. Based on the foregoing, Applicants request withdrawal of the rejection.

35 U.S.C. § 102

Claims 1, 15, 22, 132, and 133 are allegedly anticipated by US 6,420,524 ("the '524 patent) under 35 USC 102(e). SEQ ID NO:4 of the '534 patent is alleged to be identical to present SEQ ID NO:2. This rejection is respectfully traversed.

The present application derives priority through two provisional applications filed February 10, 1999 and June 15, 1999. As will be shown, all of the pending claims are entitled to a priority date of at least June 15, 1999.

The '534 patent claims priority from a series of these applications. Of these, only one, USSN 60/101,594 filed September 24, 1998, predates the June 15, 1999 date to which all of the present claims are entitled. A table identifying support for the amended claims in priority application No. 60/139,172, filed June 15, 1999 is found in the claim support table in the Appendix.

Therefore, the '534 patent is not citable under 35 USC 102(e) against the present claims except to the extent that the relevant disclosure of the '534 patent is also found in the '594 priority document. As will be shown , the '594 priority document does not disclose the claimed polypeptide lacking the signal sequence and pre-pro region (residues 1-45) of SEQ ID NO:2 purified to apparent homogeneity.

The '534 patent itself does discuss both signal and prepro regions of beta secretase (see col. 13, lines 37-47). The '534 patent also discusses a scheme to obtain cleavage of the proregion absent knowledge of the responsible enzyme. This scheme involves engineering a site for a known protease into the beta-secretase protein (see col. 18, lines 5-12). However, none of this teaching is found in the '594 priority document.

The '594 priority document lacks much of the teaching found in the '534 patent. For example, the '594 priority document characterizes the putative proteins encoded by the nucleic acids disclosed therein as apartyl proteases, but does not recognize that one is the beta secretase enzyme (the title refers to a "gamma secretase"). The '594 priority document mentions that some aspartyl proteases contain a pro region but does not disclose whether such a region exists in beta secretase itself, much less disclose that the region ends at residue 45. The '594 priority document also contains no mention of a signal sequence in the putative proteins encoded by its nucleic acids. The '594 priority document also does not disclose any actual isolation or characterization of expression products of its disclosed nucleic acids. Absent recognition of the presence or location of a signal and preproregion and a teaching to purify to homogeneity a form of beta secretase in which such sequences have been removed, the '594 application does not provide a disclosure that anticipates the present claims.

Because the '534 patent is only citable under 35 USC 102(e) to the extent its disclosure is contained in the '534 application, it does not anticipate the claims under 35 USC 102(e) for the same reasons that the '594 priority application does not anticipate.

35 U.S.C. § 103(a)

Claims 23-25, 29, and 30 are allegedly obvious over US 6,420,534 ("the '534 patent) in view of the common knowledge in molecule biology and US 6,319,689 ("the '689 patent"). The Examiner does not explicitly indicate for what each source is being cited or the motivation for combining them. For purposes of response, applicants will assume that the Examiner is relying on the '534 patent for discussing beta secretase, common general knowledge for discussing protein purification, crystallization and glycosylation, and the '689 patent for discussing peptide inhibitors. This rejection is traversed, particularly as applied to the pending claims.

The Examiner's reliance on common knowledge for methods of purification appears to stem from an incorrect assumption that the present application discloses no more than common knowledge to assist in purifying the claimed proteins to apparent homogeneity. In fact, however, the application assists in purification of the claimed proteins in several respects not found in any of the cited art or common knowledge (the '534 patent is citable only insofar as its subject matter is present in the '594 priority document, as discussed above). First, the application teaches that the first 45 residues of beta secretase constitute the signal sequence and pro-region. This teaching assists in purification of the claimed proteins because the skilled person is taught that it is such a protein and not other forms of beta secretase, which may be present, which are the desired form of the active protein. The teaching also assists in purification of the claimed proteins to apparent homogeneity in that one may design a construct which expresses only forms of beta secretase lacking amino acids 1-45, thereby avoiding the need to separate such forms from other forms containing the signal and/or pro region. Further, the application describes an additional purification step relative to those previously known employing an affinity column that has an affinity matrix a specific inhibitor of β-secretase, termed "P10—P4'staD->V" (NH_2-KTEEISEVN[sta]VAEF-CO_2H; SEQ ID NO.: 72). This purification scheme results in a beta secretase enzyme which runs as a single 70 kDa band on an SDS gel (*see* FIG. 6).

The present disclosure therefore provides specific disclosure for purification to apparent homogeneity of the claimed proteins not found in the '524 patent (insofar as its teaching is reproduced in the '594 priority application) or in common general knowledge. Because the rejection is based on the assumption that the present application relies only on art-known information to purify the claimed proteins, it is respectfully submitted that the rejection is in error and should be withdrawn.

With respect to claim 23, directed to a crystalline composition, the Examiner alleges motivation to crystallize based on a crystalline solution of the beta secretase being more stable than the soluble form of the protein and when administered to a subject is converted to the body in soluble form. This motivation is unclear as to what is meant by a "crystalline solution."

The motivation is also not found in the art. Clarification is requested if the rejection is maintained.

Claims 31, 33, 34 and 36 directed to compositions of the crystalline form of beta secretase and an inhibitor of beta-secretase are submitted to be distinguished on additional grounds. Neither, the '524 patent (insofar as citable via the '594 priority document) nor Powell provides the structure of any beta secretase substrates or inhibitors. In fact, neither the '524 patent (insofar as citable via the '594 priority document) nor Powell identify their proteins as being beta secretase. Rather, the proteins are more generally characterized as being aspartyl proteases. Without identifying any structure for a beta secretase inhibitor or substrate and without recognizing one had a beta secretase enzyme, it would not have been obvious to crystallize the enzyme with a substrate or inhibitor of beta secretase.

Obviousness-Type Double Patenting

Claims 1-4, 15, 18, 22-25, 29-34 and 36 stand provisionally rejected over USSN 724,569. However, the claims of the '569 application are directed to nucleic acids, whereas the present claims are directed to proteins. These two types of subject matter were separated by restriction requirement, so it is respectfully submitted that a double patenting rejection is not permitted under 35 USC 121.

Claims 1 and 2 stand rejected for obviousness-type double patenting over US 5,744,346 in view of common knowledge of molecular biology. The Examiner alleges that the beta secretase isolated from mammalian cells lacks the signal sequence and pre-pro region. Thus, the Examiner takes the position that present claims 1 and 2 are distinguished only in that the claims require purity to apparent homogeneity, whereas the claims of the cited patent are directed to beta secretase of a lesser degree of purity.

A double patenting rejection of the obviousness types is analogous to the nonobviousness requirement of 35 U.S.C. § 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite,* 154 USPQ 29 (CCPA 1967). A double patenting rejection should therefore make clear the differences between the inventions defined by the conflicting claims and the reasons why a person of ordinary skill in the

art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent. MPEP 804B. 1.

As the Examiner acknowledges the present claims differ from those of the '346 patent in that the present claims require beta secretase to be purified to apparent homogeneity, whereas the claims of the '346 patent specify isolated beta secretase, but do not require a state of purity of apparent homogeneity. To establish a prima facie case the Examiner must provide reasons that obtaining apparent homogeneity from an isolated preparation of lesser purity would have been obvious. It is respectfully submitted that a reference to common general knowledge is insufficient to support such a conclusion.

The present application discloses further purification of the β-secretase enzyme to apparent homogeneity by applying an isolated and purified preparation of beta secretase, such as disclosed by the '346 patent, to an affinity column that employs as its affinity matrix a specific inhibitor of β-secretase, termed "P10—P4'staD->V" (NH_2-KTEEISEVN[sta]VAEF-CO_2H; SEQ ID NO.: 72). This purification scheme results in a beta secretase enzyme which runs as a single 70 kDa band on an SDS gel (*see* FIG. 6).

Common general knowledge did not provide an inhibitor to perform affinity purification as disclosed in the present application or provide any assurance of an alternative method that would have obtained the same results. At best, common general knowledge provided a reason to try to further purify proteins in general, and a repertoire of techniques that could be applied to proteins in general.

The existing repertoire of protein purification methods requires selection from an almost infinite number of potentially available choices. Examples of available protein purification procedures include precipitation, anion-exchange chromatography, gel filtration, chromatography on hydroxyapatite columns, hydrophobic chromatography, chromatography on immobilized reactive dyes, affinity chromatography, chromatofocusing, and high-performance liquid chromatography, among others. Each of these procedures in turn has numerous variations. For example, there are many kinds of anion-exchange columns including diethylaminoethyl (DEAE), Q-polystyrene, Q-Sepharose and PEI. Which technique or combination of techniques

to apply in a given instance depends on the protein and the nature of other materials it is being separated from.

Obviousness is not established where the prior art as a whole "gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Here, common general knowledge simply provides a repertoire of techniques and no guidance which among them would likely have been successful in purifying beta secretase to apparent homogeneity. Without direction as to which of the many possible choices is likely to be successful, a prima facie case of obviousness-type double patenting has not been established.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

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